Eosinophilic Pleural Effusion Following Long-Term Asthma Remission Under Dupilumab Therapy: A Search for Clues Using Cytokine Analyses

Leonhardt J[1], Gaedtke L[1], Alkan GH[1], Hermann S[1], Kiefl R[1], Gerckens M[1,2], Lenoir A[1], Kneidinger N[1,3], Kauffmann-Guerrero D[1], Behr J[1], Milger K[1,3], Mümmler C[1,2]*

[1]Department of Medicine V, LMU University Hospital, LMU Munich, Comprehensive Pneumology Center (CPC), Member of the German Center of Lung Research (DZL), Munich, Germany
[2]Institute of Lung Health and Immunity (LHI), Comprehensive Pneumology Center (CPC), Helmholtz Munich, Member of the German Center of Lung Research (DZL), Munich, Germany
[3]Division of Respiratory Medicine, Department of Internal Medicine, Lung Research Cluster, Medical University of Graz, Graz, Austria

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Dupilumab, a monoclonal antibody against anti–IL4-receptor α, is efficacious for the treatment of several type 2 inflammatory diseases [1]. Transient, asymptomatic blood hypereosinophilia has been reported in up to 14% of patients in randomized clinical trials and real-world studies of dupilumab in patients with severe asthma [2-4]. It has been hypothesized that blockade of eosinophil migration to tissues by dupilumab results in a passive increase in the number of remaining blood eosinophils. However, several case series have described severe adverse effects associated with dupilumab-induced hypereosinophilia, including eosinophilic pneumonia, eosinophilic vasculitis, and eosinophilic pleural effusion [3,5-7]. Most of these events occurred within the first months after initiation of dupilumab [3]. Thus, some experts recommend monitoring blood eosinophils during this initial treatment period.

We present the case of a 35-year-old man with severe allergic and eosinophilic asthma. He had had early-onset allergic asthma and allergic rhinitis since childhood. Besides inhaled therapy with inhaled corticosteroids/long-acting ß-agonists/long-acting muscarinic antagonists and montelukast, he had received subcutaneous allergen immunotherapy against house dust mites and grass pollen for several years during adolescence. At the age of 16, corticosteroids were administered over several months to treat an episode of eosinophilic pneumonia and then stopped. When the patient was 21 years old, his asthma deteriorated despite high-dose inhaled corticosteroids, and he developed nasal polyps. After functional endoscopic sinus surgery, polyps reappeared within 2 years, and he

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received maintenance low-dose oral corticosteroids (OCSs) to treat frequent exacerbations. He then received omalizumab for 6 years, leading to an improvement in allergic symptoms and intermediate overall response, with blood eosinophil counts remaining elevated at 400-600/μL. Nevertheless, he still had up to 4 eosinophilic exacerbations per year requiring frequent OCS courses, and treatment was therefore switched first to mepolizumab and then to benralizumab, when these became available. Anti–IL-5/IL-5R therapies improved the exacerbations, although owing to uncontrolled chronic rhinosinusitis with nasal polyps (CRSwNP) and recurrent allergic symptoms with benralizumab, treatment was switched to dupilumab in 2019. Over the next 4 years, asthma and CRSwNP resolved, with well-controlled symptoms, normal lung function, no exacerbations, and no OCS. Intermittent increases in blood eosinophils up to 1430/μL were observed during the grass pollen season, although these subsequently declined spontaneously, with no associated adverse events. Sublingual immunotherapy for grass pollen was added in 2020, and the patient's allergic rhinitis improved. In March 2023, the patient suddenly experienced chest pain and shortness of breath. Blood tests revealed hypereosinophilia (6820/μL), and a large left-sided pleural effusion was apparent on the chest x-ray. Thoracocentesis was performed, draining 2 liters of an eosinophil-rich (35%) exudate (Figures S1A and 1B), with no evidence of pleural infection or malignancy. Testing for antineutrophil cytoplasmic antibodies was negative, and no other systemic manifestations involving the heart, skin, kidneys, or nervous system were found.

We treated the patient with prednisolone 40 mg/d for 3 days and a single dose of benralizumab to reduce the eosinophil count quickly and spare longer OCS treatment. The patient's symptoms improved quickly, and he regained good asthma control and normal lung function. As remission had not been achieved with benralizumab in the past, biological therapy was switched to tezepelumab, and to date (October 2025), the patient has been in remission (Figure S1C).

We analyzed the pleural effusion using human cytokine ELISA and compared findings with those observed for samples obtained from patients with cardiac failure (n=2), malignancy (lung cancer) (n=2), and infectious pleural effusions (n=2). Compared to effusions of other etiologies, the eosinophilic pleural effusion revealed an approximately 100-fold higher IL-13 concentration, 20-fold higher IL-5 concentration, 15-fold higher IL-4 concentration, and a higher IL-12 concentration. Values for IL-6, IL-10, and IL-17 were similar (Figure). We also analyzed patient serum from our biobank at 4 timepoints throughout the disease course under different biologics. IL-4, IL-5, and IL-13 levels in serum remained stable with dupilumab (Figure S1C). At the time of the eosinophilic pleural effusion, IL-5 peaked, while IL-4 and IL-13 remained unchanged.

The patient gave his written informed consent for the publication of this case report. All biosamples were

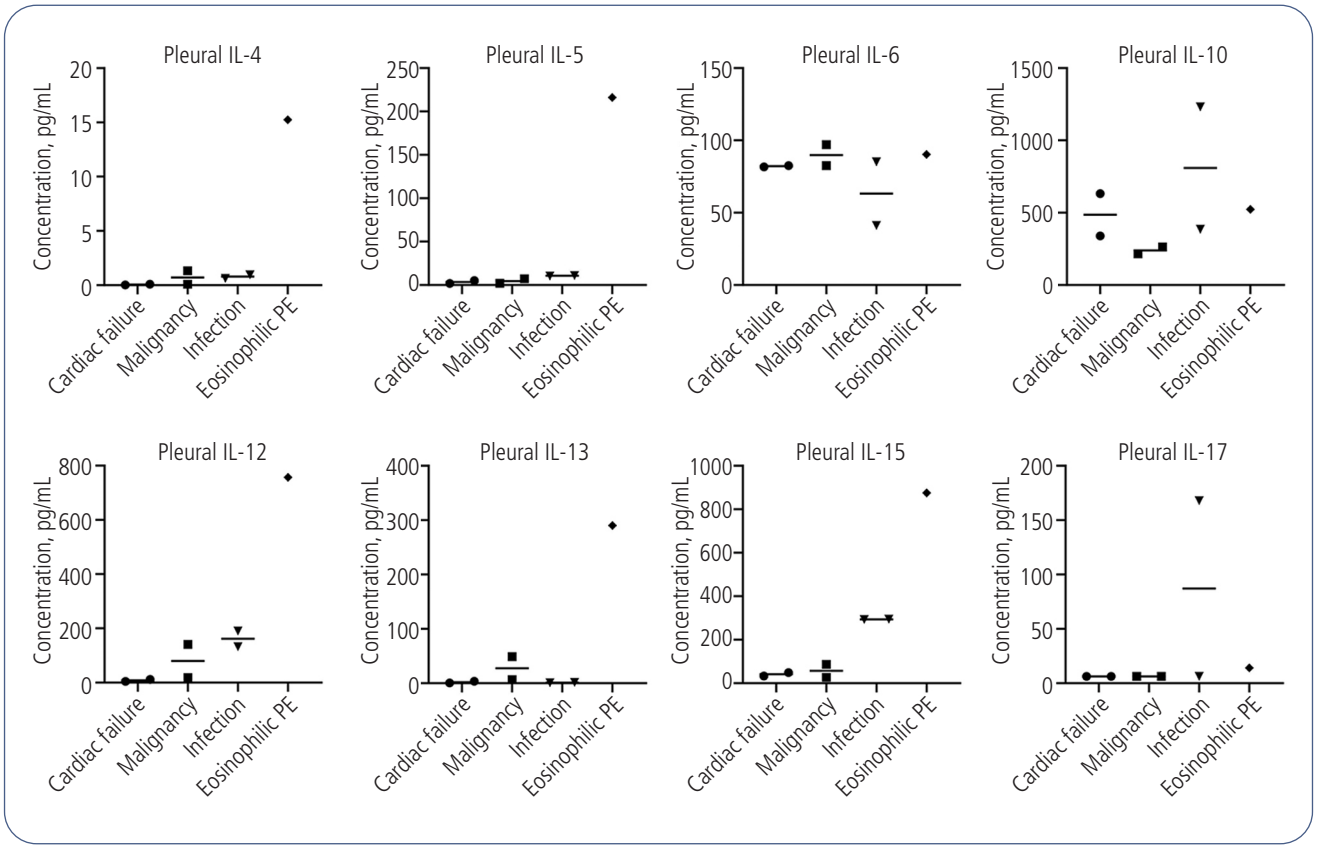


Figure. Cytokine measurements in pleural effusion from a patient with dupilumab-associated eosinophilic pleural effusion (PE) and in other pleural effusions (disease controls).

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obtained from the CPC bioarchive with the permission of the participating patients, who gave their written informed consent (ethics vote LMU 382–10).

Studies investigating the biological drivers of eosinophilia and its consequences in dupilumab-treated patients are lacking. A meta-analysis by Wechsler et al [2] showed transient hypereosinophilia to be common during dupilumab treatment, typically occurring during the first 6 months. Caminati et al [3] reported similar data for a real-world cohort from a severe asthma population, with the recommendation of eosinophil monitoring until 8 months after initiation of treatment. Further, Lommatzsch et al [5] described an eosinophilic pleural effusion occurring early after treatment with dupilumab. The present case, however, demonstrates that eosinophilic adverse events may even occur after years of remission with dupilumab. An identifiable trigger for the event could not be found.

Dupilumab proved highly effective in controlling the patient's disease for several years, with asthma in remission and low FeNO levels, even while he experienced hypereosinophilia, indicating successful suppression of IL-4R signaling. During the eosinophilic pleural effusion, a marked increase in serum IL-5 levels was observed, whereas serum IL-4 and IL-13 levels remained stable. A key question that arises is whether the eosinophilic event should be considered a dupilumab-related adverse event or, more likely, a manifestation of inherent (genetic) susceptibility, which dupilumab was only able to partly control. In agreement with the latter, Ezekwe et al [8] demonstrated a higher risk of eosinophilic adverse events in dupilumab-treated patients with hypereosinophilic syndrome (HES), suggesting that dupilumab's mode of action might not be sufficient in these strongly eosinophil-driven conditions. Although the patient in the present case did not have an established diagnosis of HES, his past medical history did show eosinophilic pneumonia, thus possibly leaving him susceptible to dupilumab-associated eosinophilic organ manifestations. According to current proposals, the disease could be classified as HES with single organ involvement, since there were no signs of vasculitis, which is required for a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) [9]. Importantly, we demonstrated very high concentrations for type 2 cytokines (IL-4, IL-5, IL-13) and other inflammatory cytokines in the pleural fluid, suggesting that dupilumab was unable to control an underlying disease flare and that it was not effective in blocking eosinophil migration into the pleural space. Similarly, other drugs, such as montelukast, have previously been suspected of triggering EGPA [10]. However, these observations may be confounding, as therapy with montelukast was typically escalated in patients with worsening disease [10].

Future studies should investigate the underlying drivers of hypereosinophilia in blood, respiratory fluids, and tissues by comparing patients with dupilumab-induced hypereosinophilia and those without.

In conclusion, hypereosinophilic complications, which are possibly associated with dupilumab, may arise even after years of successful therapy. A history of any systemic eosinophilic manifestation may be a risk factor that warrants consideration of other type 2 biologics with an eosinophil-lowering mode of action.

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Conflicts of Interest

MG received a travel grant from Chiesi outside the submitted work.

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NK reports personal fees and speaker fees from GSK and AstraZeneca outside the submitted work.

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ORCID

Michael Gerckens https://orcid.org/0000-0002-2251-4382
Alexandra Lenoir https://orcid.org/0000-0003-2189-6507
Nikolaus Kneidinger https://orcid.org/0000-0001-7583-0453
Jürgen Behr https://orcid.org/0000-0002-9151-4829
Katrin Milger https://orcid.org/0000-0003-2914-8773
Carlo Mümmler https://orcid.org/0000-0002-2501-3356

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Katrin Milger
Division of Respiratory Medicine
Department of Internal Medicine
Medical University of Graz
Auenbruggerplatz 15
8036 Graz, Austria
E-mail: katrin.milger-kneidinger@medunigraz.at

Carlo Mümmler
Department of Medicine V
Ludwig-Maximilians-University of Munich (LMU)
Marchioninistr. 15
81377 Munich, Germany
E-mail: carlo.muemmler@med.uni-muenchen.de

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